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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,466	09/05/2007	Stephen Jay Anderson	P5201R1	3697

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EXAMINER	
SHEN, WU CHENG WINSTON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,466	ANDERSON ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *247-386* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *247-386* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The claim amendments filed on 09/21/2006 have been entered. Claims 1-246 are cancelled. Claims 247-386 are newly added. Claims 247-386 are pending in the instant application and are subject to restriction in this office action.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 247-267, drawn to a method of identifying a phenotype associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal; and (c) comparing the measured physiological characteristic with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that

differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal (claim 247).

II. Claims 268-271, drawn to an isolated cell derived from a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide (claim 268).

III. Claims 272-291, drawn to a method of identifying an agent that modulates a *phenotype* associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

IV. Claims 292-295, drawn to an agent identified by the method of claim 272

V. Claim 296 and 297, drawn to a method of identifying an agent that modulates a *physiological characteristic* associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO 19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) measuring a physiological characteristic exhibited by the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic exhibited by the non-human transgenic animal that differs from the physiological characteristic exhibited by the wild-type animal is identified as a physiological characteristic associated with gene disruption; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the physiological characteristic associated with gene disruption is modulated.

VI. Claims 298-301, drawn to an agent identified by the method of Claim 296.

VII. Claims 302-308, drawn to a method of identifying an agent which modulates a *behavior* associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO 1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO 19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide;

(b) observing the behavior exhibited by the non-human transgenic animal of (a); (c) comparing the observed behavior of (b) with that of a gender matched wild-type animal, wherein the observed behavior exhibited by the non-human transgenic animal that differs from the observed behavior exhibited by the wild-type animal is identified as a behavior associated with gene disruption; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the agent modulates the behavior associated with gene disruption.

VIII. Claims 309-312, drawn to an agent identified by the method of claim 302.

IX. Claims 313-331, drawn to a method of identifying an agent that ameliorates or modulates a neurological disorder; a cardiovascular, endothelial or angiogenic disorder; an eye abnormality; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality associated with a disruption in a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) administering a test agent to said non-human transgenic animal; and (c) determining whether said test agent ameliorates or modulates the neurological disorder; cardiovascular, endothelial or angiogenic disorder; eye abnormality; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality in the non-human transgenic animal.

X. Claims 332 and 333, drawn to an agent identified by the method of claim 313 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein said agonist or antagonist is *not* an antibody.

XI. Claims 334 and 335, drawn to an agent identified by the method of claim 313 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein the agonist or antagonist is an anti-PRO224, anti- PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti- PRO230, anti-PRO 178, anti-PRO 1199, anti-PRO4333, anti-PRO 1336, anti-PRO 19598, anti- PRO 1083, anti-hu TRPM2 or anti-PRO 1801 antibody.

XII. Claims 336, drawn to a therapeutic agent identified by the method of claim 313

XIII. Claims 337, drawn to a method of identifying an agent that modulates the expression of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising: (a) contacting a test agent with a host cell expressing a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; and (b) determining whether the test agent modulates the expression of the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide by the host cell.

XIV. Claims 338-339, drawn to an agent identified by the method of claim 337 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein said agonist or antagonist is *not* an antibody.

XV. Claims 340-341, drawn to an agent identified by the method of claim 337 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein the agonist or antagonist is an anti-PRO224, anti- PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti- PRO230, anti-PRO 178, anti-PRO 1199, anti-PRO4333, anti-PRO 1336, anti-PRO 19598, anti- PRO 1083, anti-hu TRPM2 or anti-PRO 1801 antibody.

XVI. Claims 342-343, drawn to a method of evaluating a therapeutic agent capable of affecting a condition associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO 19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a condition resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-

human transgenic animal of (a); and (e) evaluating the effects of the test agent on the identified condition associated with gene disruption in the non-human transgenic animal.

XVII. Claim 344, 345, and 348, drawn to a therapeutic agent identified by the method of Claim 342 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801polypeptide, wherein said agonist or antagonist is *not* an antibody .

XVIII. Claim 346, 347, and 348, drawn to a therapeutic agent identified by the method of Claim 342 which is an agonist or antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801polypeptide, wherein the agonist or antagonist is an anti-PRO224, anti- PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti- PRO230, anti-PRO 178, anti-PRO 1199, anti-PRO4333, anti-PRO 1336, anti-PRO 19598, anti- PRO 1083, anti-hu TRPM2 or anti-PRO 1801 antibody.

XIX. Claims 349-366 (in part, pertaining to treatment or amelioration), drawn to a method of *treating or ameliorating* a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO224, PRO9783, PRO 1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising administering to a subject in need of such treatment whom may already have the disorder, or may be prone to have the disorder or may be in whom the disorder is to be prevented, a therapeutically effective amount of the

therapeutic agent of Claim 336, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

XX. Claims 349-366 (in part, pertaining to prevention), drawn to a method of *preventing* a neurological disorder; cardiovascular, endothelial or angiogenic disorder; immunological disorder; oncological disorder; bone metabolic abnormality or disorder, or embryonic lethality associated with the disruption of a gene which encodes for a PRO224, PRO9783, PRO 1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising administering to a subject in need of such treatment whom may already have the disorder, or may be prone to have the disorder or may be in whom the disorder is to be prevented, a therapeutically effective amount of the therapeutic agent of Claim 336, or agonists or antagonists thereof, thereby effectively treating or preventing or ameliorating said disorder.

XXI. Claim 367 (in part, pertaining to administrating agent of claim 292), drawn to a method of modulating a phenotype associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already have the phenotype, or may be prone to have the phenotype or may be in whom the phenotype is to be prevented, an effective amount of the *agent of claim 292*, thereby effectively modulating the phenotype.

XXII. Claim 367 (in part, pertaining to administrating agonists or antagonists of the agent of claim 292), drawn to a method of modulating a phenotype associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the

method comprising administering to a subject whom may already have the phenotype, or may be prone to have the phenotype or may be in whom the phenotype is to be prevented, an effective amount of *agonists or antagonists of the agent of claim 292*, thereby effectively modulating the phenotype.

XXIII. Claim 368 (in part, pertaining to administrating agent of claim 298), drawn to a method of modulating a physiological characteristic associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already exhibit the physiological characteristic, or may be prone to exhibit the physiological characteristic or may be in whom the physiological characteristic is to be prevented, an effective amount of the agent of claim 298, thereby effectively modulating the physiological characteristic.

XXIV. Claim 368 (in part, pertaining to administrating agonists or antagonists of the agent of claim 298), drawn to a method of modulating a physiological characteristic associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already exhibit the physiological characteristic, or may be prone to exhibit the physiological characteristic or may be in whom the physiological characteristic is to be prevented, an effective amount of agonists or antagonists of the agent of claim 298, thereby effectively modulating the physiological characteristic.

XXV. Claim 369 (in part, pertaining to administrating agent of claim 309), drawn to a method of modulating a behavior associated with a disruption of a gene which

encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already exhibit the behavior, or may be prone to exhibit the behavior or may be in whom the exhibited behavior is to be prevented, an effective amount of the agent of claim 309, thereby effectively modulating the behavior.

XXVI. Claim 369 (in part, pertaining to administrating agonists or antagonists of agent of claim 309), drawn to a method of modulating a behavior associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may already exhibit the behavior, or may be prone to exhibit the behavior or may be in whom the exhibited behavior is to be prevented, an effective amount of agonists or antagonists of the agent of claim 309, thereby effectively modulating the behavior.

XXVII. Claims 370 (in part, pertaining to administrating agent of claim 338), drawn to a method of modulating the expression of a PRO224, PRO9783, PROl108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO 19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising administering to a host cell expressing said PRO224, PRO9783, PRO 1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, an effective amount of the agent of claim 338, thereby effectively modulating the expression of said polypeptide

XXVIII. Claims 370 (in part, pertaining to administrating agonists or antagonists of agent of claim 338), drawn to a method of modulating the expression of a PRO224, PRO9783, PROl108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO 19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising administering to a host cell expressing said PRO224, PRO9783, PRO 1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, an effective amount of agonists or antagonists of the agent of claim 338, thereby effectively modulating the expression of said polypeptide

XXIX. Claim 371 (in part, pertaining to administrating agent of claim 344), drawn to a method of modulating a condition associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may have the condition, or may be prone to have the condition or may be in whom the condition is to be prevented, a therapeutically effective amount of the therapeutic agent of claim 344, thereby effectively modulating the condition.

XXX. Claim 371 (in part, pertaining to administrating agonists or antagonists of agent of claim 344), drawn to a method of modulating a condition associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject whom may have the condition, or may be prone to have the condition or may be in whom the condition is to be prevented, a therapeutically effective amount of agonists or antagonists of the

therapeutic agent of claim 344, or thereof, thereby effectively modulating the condition.

XXXI. Claims 372-374, drawn to a method of identifying an agent that mimics a condition or phenotype associated with a disruption in a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the gender matched wild-type animal is identified as a condition or phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to said gender matched wild-type animal; and (e) determining whether said test agent mimics the condition or phenotype initially observed in the non-human transgenic animal.

XXXII. Claims 375 and 376, drawn to an agent identified by the method of claim 372 which is an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein said antagonist is *not* an antibody.

XXXIII. Claim 377, drawn to an agent identified by the method of claim 372 which is an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu

A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein the antagonist is an anti-PRO224, anti- PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti- PRO230, anti-PRO178, anti-PRO1199, anti-PRO4333, anti-PRO1336, anti-PRO19598, anti- PRO1083, anti-hu TRPM2 or anti-PRO1801 antibody.

XXXIV. Claims 378-380 (in part, pertaining to the agent of claim 375), drawn to a method of mimicking a condition or phenotype associated with a disruption of a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising administering to a subject in whom the condition or phenotype is to be mimicked, an effective amount of the agent of claim 375 which said antagonist is *not* an antibody, thereby effectively mimicking the condition or phenotype.

XXXV. Claims 378-380 (in part, pertaining to antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide), drawn to a method of mimicking a condition or phenotype associated with a disruption of a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising administering to a subject in whom the condition or phenotype is to be mimicked, an effective amount of an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, thereby effectively mimicking the condition or phenotype, thereby effectively mimicking the condition or phenotype.

XXXVI. Claim 381, drawn to a method of evaluating a therapeutic agent capable of mimicking a condition or phenotype associated with a disruption of a gene which encodes a PRO224, PRO9783, PROll08, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PROl199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the gender matched wild-type animal is identified as a condition or phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to said gender matched wild-type animal of (c); and (e) evaluating the ability of the test agent to mimic the condition or phenotype associated with gene disruption in the non-human transgenic animal.

XXXVII. Claim 382, 383, and 385, drawn to a therapeutic agent identified by the method of claim 381 which is an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein said antagonist is *not* an antibody.

XXXVIII. Claims 384 and 385, drawn to a therapeutic agent identified by the method of claim 381 which is an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, wherein the antagonist is an anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000,

anti-PRO240, anti-PRO943, anti-hu A33, anti- PRO230, anti-PRO 178, anti-PRO 1199, anti-PRO4333, anti-PRO 1336, anti-PRO 19598, anti- PRO 1083, anti-hu TRPM2 or anti-PRO 1801 antibody.

XXXIX. Claim 386, drawn to a method of mimicking a condition or phenotype associated with a disruption of a gene which encodes a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PROl199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, the method comprising administering to a subject in whom the condition or phenotype disorder is to be mimicked, a therapeutically effective amount of the therapeutic agent of Claim 382, or an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PROl199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide, thereby effectively mimicking the condition or phenotype.

(A) Each Group of Groups I-XXXIX is subjected to the **further restrictions to a specific PRO** (i.e. PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PROl199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2, and PRO1801 polypeptide) encoded by specific gene. It is noted that the Figures of instant specification disclose SEQ ID No of the nucleotide sequences corresponding to the gene encoding PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PROl199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide. This further restriction is applicable to claims reciting an antagonist of a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2, and PRO1801 polypeptide; and

applicable to claims reciting anti-PRO224, anti-PRO9783, anti-PRO1108, anti-PRO34000, anti-PRO240, anti-PRO943, anti-hu A33, anti- PRO230, anti-PRO 178, anti-PRO 1199, anti-PRO4333, anti-PRO 1336, anti-PRO 19598, anti- PRO 1083, anti-hu TRPM2, and anti-PRO 1801 antibody. This is **not** a requirement for election of species.

MPEP 803.04 states:

> Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq. Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided sua sponte to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See Examination of Patent Applications Containing Nucleotide Sequences, 1192 O.G. 68 (November 19, 1996).

Although the MPEP deems that up to ten nucleotide sequences may be searched without restriction, the Commissioner has stated that, "The Office has reconsidered the policy set forth in the 1996 Notice in view of changes in the complexity of applications filed, the types of inventions claimed and the state of the prior art in this technology since that time. Because of these changes, the search and examination of up to ten molecules described by their nucleotide sequence often consumes a disproportionate amount of Office resources over that expended in 1996. Consequently, with this Notice the Office rescinds the partial waiver of 37 CFR 1.141 et seq. for restriction practice in national applications filed under 35 U.S.C. 111(a), and 37 CFR 1.475 et seq. for unity of invention determinations in both PCT international applications and the resulting national stage applications under 35 U.S.C. 371." See Examination of Patent Applications Containing Nucleotide Sequences 1316 OG 122 (March 27, 2007). **For this reason, restriction to ONE SEQUENCE is being applied to all applications at this time.**

(B) In addition to **(A)** listed above, the following claims are subjected to further restriction.

Claims 249, 271, 273, 313, and 343 are further restricted to a specific genus of diseases, which includes (i) the genus of a neurological disorder; (ii) the genus of a cardiovascular, endothelial or angiogenic disorder; (iii) the genus of an eye abnormality; (iv) an immunological disorder; (v) the genus of an oncological disorder; (vi) the genus of a bone metabolic abnormality or disorder; (vii) the genus of a lipid metabolic disorder; and (viii) the genus of a developmental abnormality. Each genus of diseases affects distinct tissues and has distinct underlying causes, and each genus of diseases comprises multiple species of different diseases.

This is **not** a requirement for election of species.

3. The inventions listed of Groups I-XXXIX do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Applicant's claims encompass multiple inventions, multiple products (cells, antibody, agents, therapeutic agents) with distinct structures and functions, and multiple methods (methods of identifying a phenotype in a non-human transgenic animal, methods of identifying an agent that modulates a phenotype associated with a disruption of a gene, a method of identifying an agent that modulates a physiological characteristic associated with a disruption of a gene, a method of identifying an agent which modulates a behavior associated with a disruption of a gene, methods of evaluating a therapeutic agent capable of affecting a condition associated with a disruption of a gene, a method of treating or ameliorating a disorder, and methods of preventing a disorder etc) with distinct goals, methods steps, and technical consideration; and do

not have a special technical feature which link the inventions one to the other, and lack unity of invention. Furthermore, there is no common technical feature in all groups.

4. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

(i) Claims 250-255, 274-279, 314-319, and 350-355 recite various neurological disorders and these various neurological disorders are different species because each class neurological disease has different underlying cause (etiology), pathological phenotypes, and potential treatments.

(ii) Claims 256-262, 280-286, 320-326, and 356-362 recite various eye abnormalities and these various eye abnormalities are different species because each class neurological disease has different underlying cause (etiology), pathological phenotypes, and potential treatments.

(iii) Claims 263, 287, 327, and 363 recites various developmental abnormalities (i.e. recited embryonic lethality and reduced viability) and these various developmental abnormalities are different species because each class neurological disease has different underlying cause (etiology), pathological phenotypes, and potential treatments.

(iv) Claims 264, 288, 328, and 364 recites various cardiovascular, endothelial or angiogenic disorders and these various cardiovascular, endothelial or angiogenic disorders are different species because each class neurological disease has different underlying cause (etiology), pathological phenotypes, and potential treatments.

(v) Claims 265, 289, 329, and 365 recite various immunological disorders and these various immunological disorders are different species because each class neurological disease has different underlying cause (etiology), pathological phenotypes, and potential treatments.

(vi) Claims 266, 290, 330, and 366 recite various bone metabolic abnormalities or disorders and these various bone metabolic abnormalities or disorders are different species because each class neurological disease has different underlying cause (etiology), pathological phenotypes, and potential treatments.

(vii) Claims 267, 291, 297, and 331 recite various physiological characteristics and these various physiological characteristics are different species because each physiological characteristic has different underlying molecular, cellular, and biochemical basis that is detected and/or analyzed by different assays.

(viii) Claims 303-308 recite various behaviors and these various behaviors are different species because each behavior of a non-human transgenic animal has different underlying genetic disruption of a gene and is detected and/or analyzed by different assays.

Applicant is required, in reply to this action, to elect a single species, for each one of **(i)** to **(viii)** listed above, to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election. It is noted that the election of species **must** be consistent with the election of invention (i.e. restriction).

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

MPEP 1893.03(d) Unity of Invention Rejoinder

5. MPEP 1893.03(d) states: If an examiner (1) determines that the claims lack unity of invention and (2) requires election of a single invention, when all of the claims drawn to the elected invention are allowable (i.e., meet the requirements of 35 U.S.C. 101, 102, 103 and 112), the nonelected invention(s) should be considered for rejoinder. Any nonelected product claim that requires all the limitations of an allowable product claim, and any nonelected process claim that requires all the limitations of an allowable process claim, should be rejoined. See MPEP § 821.04 and § 821.04(a). Any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b).

6. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction were not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103 (a) of the other invention.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632